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PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:	Examiner: BADIO
JOHN SEFTON	
Serial No: 09/367,712	Group Art Unit: 1616
Filed: August 18, 1999	
For: TAZAROTENE AND CORTICO-STERIOD TREATMENT FOR PSORIASIS	Date: January 8, 2001

Box AF
Honorable Commissioner of Patents and Trademarks
Washington, D.C. 20231

BRIEF ON APPEAL

Dear Sir:

This appeal is taken from the final rejection of all of the claims in an Examiner's action mailed July 21, 2000. Oral hearing is waived.

(1) STATUS OF CLAIMS

Claims	Status
1-13	Rejected under 35 USC § 103 as being obvious

(2) STATUS OF POST FINAL ACTION AMENDMENTS

Amendment, filed on October 16, 2000, after final rejection is pending entry until filing of Appeal Brief. A further amendment is filed herewith to correct an obvious error in claim 10. The appended claims assume that this further amendment will be entered.

(3) CONCISE SUMMARY OF THE INVENTION

The present invention relates to a method of treating psoriasis in humans with a combination of tazarotene, preferably a gel, and a corticosteroid, preferably a cream. Data has been developed by the named inventor showing that the mid- or high-potency corticosteroids in combination with tazarotene provide a more effective treatment than tazarotene, alone, or in combination with a low-potency corticosteroid. It is believed that the combination treatment of tazarotene and a mid- or high-potency corticosteroids show a synergistic effect which cannot be predicted.

(4) ISSUES PRESENTED FOR REVIEW

Obviousness

Claims 1-13 have been rejected under 35 USC § 103 as being unpatentable over Yamamoto '906 and Nagpal et al. '279 in combination. Claim 2 has been rejected under 35 USC § 103 as being unpatentable over Smith '074 or Sequeira et al. '529 in combination with Nagpal et al '279.

The Examiner has argued that:

Yamamoto '906 discloses the use of any adrenocortical hormone in treatment of psoriasis

Yamamoto '906 discloses a number of preferred compounds such as betamethasone valerate and fluocinolone (see, column 4, Table 5).

Nagpal et al. '279 disclose the use of tazarotene in the treatment of psoriasis.

Smith '074 and Sequeira et al. '529 disclose the use of corticosteroids, such as alclometasone dipropionate and betamethasone dipropionate in the treatment of psoriasis.

The Examiner concludes that it would have been obvious to a person having ordinary skill in the art at the time the instant invention was made to combine tazarotene and an adrenocortical hormone and to use the resulting composition for treating psoriasis because the results obtained thereby would have been expected.

(5) GROUPING OF CLAIMS

Group I, Obviousness includes claims 1-3, 5 and 12.

Group II, Obviousness includes claims 6-8, 10,11 and 13.

(6) ARGUMENT

OBVIOUSNESS

The Rejection of the Claims of Group I and Group II Under 35 USC § 103

The Examiner has rejected claims 1-5, 12 and claims 6-11 13 under 35 USC § 103 as being unpatentable over Yamamoto '906 and Nagpal et al. '279 in combination. The Examiner correctly states that Yamamoto '906 discloses a method of treating psoriasis with the use of any adrenocortical hormone and that Nagpal et al. '279 disclose a method of treating psoriasis with tazarotene.

There is no motivation found in either reference for the combination of tazarotene and a corticosteroid. However, to further distinguish the Yamamoto reference from the claimed subject matter, the applicant has amended the claims to include only mid- to high-potency corticosteroid.

The applicant does not disagree with the Examiner's summarization of the prior art. However, the Examiner's conclusion that "it would have been obvious to the skilled artisan that Yamamoto recognizes the use of both mid and high potency corticosteroids in the treatment of psoriasis based on the exemplified compounds (see col. 2, lines 1-19). The determination of the degree of efficacy of each of these compounds in treating psoriasis involves only routine analysis and is within the level of skill of the ordinary artisan. The determination of which combination of corticosteroid and tazarotene is most effective and/or which results in the lowest adverse effect is also within the level of skill of the ordinary artisan" is incorrect.

The Examiner's final argument is that, since both tazarotene and corticosteroids are known agents for treating psoriasis, it would have been obvious to a person having ordinary skill in the art at the time the instant invention was made to combine the two agents into a single composition because the resulting composition would be expected to be useful for treating psoriasis. The Examiner specifically states her finding, "that mid- or high-potency corticosteroids in combination with tazarotene gives the best results while achieving the lowest adverse effects is not considered a patentable invention." This is not the standard for obviousness. This test appears to revert to the requirement for synergy when the invention is predicated on the combination of

known components. Synergy is no longer the test for obviousness when the invention is a combination of old elements. Note, for example, the statement in *In re Certain Steel Rod Treating Apparatus* (ITC 1981), 215 USPQ 237 "We conclude that the better view is that obviousness, not synergism, is the sole criterion for patentability under section 103. Reading Sakraida and Anderson's Black Rock to mean that combination patents are to be tested by the different and more rigorous standard of synergism does not square with the language of section 103 or *Graham v. John Deere Co., In Republic Industries, Inc. v. Schlage Lock Co.*, 592 F.2d 963, 971, 200 USPQ 769, 778-779 (7th Cir. 1979), the Seventh Circuit noted that: "In enacting section 103, Congress expressly mandated non-obviousness, not synergism, as the sole test for the patentability of novel and useful inventions: indeed, synergism is not even mentioned in the Patent Act of 1952."

The test for obviousness of a combination invention is whether one of ordinary skill in the art would have been motivated to make the combination. Applicants have argued that the combination of tazarotene and corticosteroid is not suggested by any of the cited references

The applicant argues that is clear from the background of the Art that there is great interest in formulating topical compositions for treating psoriasis.

When an obviousness determination is made, "there must be a showing of some 'teaching, suggestion, or reason' to combine the references:, *Winner Intl. Royalty Corp. v. Wang* 53 USPQ2d 1586. Yamamoto '906 teaches away from the use of corticosteroids at the usual clinical doses in combination with active ingredients. Yamamoto '906 utilizes hyaluronic acid to reduce the concentration of the corticosteroid applied to one-half to about one-tenth (see col. 2, lines 27-59) and suggests that this is the method to reduce irritation. There is no suggestion to combine a corticosteroid with an active agent wherein the corticosteroid concentration is maintained at an effective amount. As an example, an effective and usual concentration fluocinonide (high potency corticosteroid) is 0.05%. This concentration causes irritation and the Yamamoto '906 dilutes this concentration to 0.015% or 0.005% to reduce the adverse corticosteroid-induced effects. Similar examples can be cited for betamethasone dipropionate, a mid potency corticosteroid, and clobetasol propionate, a super potency corticosteroid (see col. 4, lines 32-55, Table 5).

The Applicant has demonstrated that mid- or high-potency corticosteroids in combination with tazarotene exhibit a synergistic effect that provide a more

effective treatment of psoriasis than tazarotene, alone, or with a low-potency corticosteroid. (See lines 20-23 of page 9 of the present specification.).

The unpredictable results for the combination of the mid- or high-potency corticosteroids with tazarotene are given in Example 1. (See page 10, line 28 through page 11, line 5 of the present specification and Figure 1.)

Based on effectiveness of each individual component and the synergistic effect of the combination of the two components in an unpredictable technology (Testing of the combinations was required to demonstrate effectiveness or lack thereof.), there is no *prima facie* obviousness of predictable results. One must consider the predictability of the technology, MPEP 2144.08(e). It is well known that the field of pharmaceuticals is unpredictable. Even if two separate pharmaceuticals are indicated for the same treatment, success is not known until both pharmaceuticals are tried. In an unpredictable technology, it is less likely that structurally similar species will render a claimed species obvious, because it may not be reasonable to infer that the species would share similar properties. This is the epitome of the incorrect obviousness standard of obvious to try. See e.g., *In re O'Farrell* 7 USPQ2d 1680 (Fed. Cir. 1988), *In re Merck & Co., Inc.* 231 USPQ 381 (Fed. Cir. 1986), *In re May* 197 USPQ 601, 611 (CCPA 1978).

The Examiner has rejected Claim 2 under 35 U.S.C. 103(a) as being unpatentable over Smith ('074) or Sequeira et al. ('529) in combination with Nagpal et al. ('279). The Examiner admits that Smith and Sequeira et al. teach only the use of corticosteroids, such as alclometasone dipropionate and betamethasone dipropionate in the treatment of psoriasis and Nagpal et al. teach only the use of tazarotene in the treatment of psoriasis. The Examiner argues that "the ordinary artisan would be motivated to use combination treatment". When applying 35 U.S.C. 103, one must adhere to the following tenet: "(C) The references must be viewed without the benefit of impermissible hindsight vision afforded by the claimed invention", MPEP 2141. As testing of the combinations was required to demonstrate effectiveness or lack thereof., there is no *prima facie* obviousness of predictable results. One must consider the predictability of the technology, MPEP 2144.08(e). It is well known that even if two separate pharmaceuticals are indicated for the same treatment, success cannot be predicted until both pharmaceuticals are tried.

The claims in Group I for treating proliferative skin diseases are supported by the data provided in working Examples I & II in the present

specification. In a large (over 350 patients) multicenter study it was found that the treatment group with tazarotene/mid potency combination achieved clinically significant reductions in plaque elevation, psoriasis improvement, reduction in scaling and erythema, indicators of proliferative skin diseases. These improvements were retained during the follow-up period. The incidence of adverse effects fell from 42% in the tazarotene/placebo group to 32% for the tazarotene/mid potency corticosteroid (mometasone furoate and alclometasone dipropionate as given in claim 5). Claim 2 is also supported by the data provided in the two working examples. Claim 2 includes a high potency corticosteroid, fluocinonide. The data provided in Example I illustrated that the treatment group with tazarotene/high potency combination achieved a treatment success rate of 75% compared to the other treatment combinations and achieved initial treatment success faster (median time of 2 weeks as compared with 4 weeks for the other combinations) while the incidence of adverse effects was 31%. Claims 2 and 5 are additionally supported by working Example II in which both mometasone furoate and fluocinonide were associated with significantly higher treatment success rates, significantly greater reductions in scaling, erythema, and overall lesional severity with a corresponding decrease in adverse effect incidences when treating proliferative skin diseases.

The claims in Group II for treating psoriasis are supported by the data provided in working Examples I and II in the present specification. The data provided in Example I showed that tazarotene/high potency combination achieved a success rate of 75% and tazarotene/mid potency combination had a success rate of $\geq$ 60% in clinical improvement in psoriasis. The unexpected and surprising finding was the decrease in overall incidence of adverse events with increased corticosteroid potency. In Example II, the use of tazarotene in combination with either a mid (mometasone furoate) or a high potency (fluocinonide) corticosteroid was associated with a higher success treatment rate along with a decreased incidence of adverse effects. Figure 2 in the present specification illustrates clearly the unexpected and unpredictable success of use of the high-potency corticosteroid, both during and after the treatment period.

Even if the broad claims, i.e. Claims 1 and 6 are held to be unpatentable over the above rejections, Claims 2, 5, 10 which cover specific corticosteroids which are shown in Examples 1 and 2 to have synergistic effects in combination with tazarotene for treating hyperproliferative disease, e.g. psoriasis, are

separately patentable. Also Claims 12 and 13, which are limited to synergistic combinations of high potency corticosteroids and tazarotene are shown in Examples 1 and 2 to be unexpectedly better than all other corticosteroids, including medium potency corticosteroids, are separately patentable, even if the remaining claims are unpatentable over the prior art.

In view of the above, the Board is asked to reverse the Examiner's holding of all of the pending claims in Groups I or in Group II as unpatentable and direct the Examiner to pass the claims in to issue.

Respectfully submitted,

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C H O'Donohue Date Signed: January 8, 2001

Cynthia H. O'Donohue, Reg. No.44980, Agent for Applicant

(7) APPENDIX

CLAIMS:

1. A method for treating proliferative skin diseases comprising the administration of an effective amount of tazarotene and an effective amount of a mid- or high-potency corticosteroid.

2. The method of claim 1 wherein said corticosteroid is selected from the group consisting of alclometasone dipropionate, mometasone furoate, fluocinonide, and betamethasone valerate.

3. The method of claim 1 wherein tazarotene is applied as a 0.1% gel.

4. Cancelled

5. The method of claim 2 wherein said corticosteroid is selected from the group consisting of mometasone furoate and alclometasone dipropionate.

6. A method for treating psoriasis in a human subject by topically applying to the psoriatic skin of said subject an effective amount of tazarotene and an effective amount of a mid- or high-potency corticosteroid.

7. The method of claim 6 wherein tazarotene is applied as a 0.1% gel.

8. The method of claim 7 wherein said corticosteriod is a cream.

9. Cancelled

10. The method of claim 6 wherein said corticosteroid is selected from the group consisting of mometasone furoate and fluocinonide.

11. The method of claim 6 wherein tazarotene is administered once daily in the evening and the corticosteroid is administered once daily in the morning.

12. The method of claim 1 wherein said corticosteroid is a high potency corticosteroid.

13. The method of claim 6 wherein said corticosteroid is a high potency corticosteroid.